CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-165

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To:	NDA 22-165
From:	Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date:	8-Oct-2008
Drug:	Diclofenac potassium for oral solution
Route of administration:	Oral
Strength:	50 mg
Subject:	**Approval** recommendation for NDA 22-165

Introduction: Diclofenac (as the potassium or sodium salt) is a widely marketed NSAID with analgesic, anti-inflammatory and antipyretic properties. Currently, a number of dosage forms that contain the active moiety are marketed within the U.S. Approved products include Cataflam® (diclofenac potassium) Tablets, Voltaren® (diclofenac sodium) Delayed Release Tablets and Opthalmic Drops, Voltaren® XR (diclofenac sodium) Extended Release Tablets and Solaraze® (diclofenac sodium) Topical Gel. All of the products named above except Solaraze® are marketed by Novartis Pharmaceuticals; Solaraze is marketed by Bioglan Pharmaceuticals. In the current NDA, ProEthic proposes to market an oral, water-soluble, powdered formulation of diclofenac potassium that is intended for treatment of migraine with or without aura in adults. The product will be available as single dose packets containing 50 mg diclofenac potassium and inactive excipients. (b) (4)

Drug Substance: The active ingredient, diclofenac potassium, is a well characterized small molecule with molecular formula $C_{14}H_{10}Cl_2KNO_3$ and molecular weight 334.24. Diclofenac potassium is slightly soluble in water under acidic pH; solubility increases as the pH increases to 7.5. The drug substance is manufactured by (b) (4) and all the CMC information related to the drug substance is referenced to DMF (b) (4). The DMF was reviewed in this review cycle and found to be adequate to support the current NDA. The drug substance acceptance specification established by the applicant includes testing for appearance, identification (by IR and NIR), identification for the counter ion potassium, appearance of solution, heavy metals, loss on drying, assay and related substance.

Drug product: The drug product will be available in single dose units, 'sachets', of 50 mg of Diclofenac Potassium blended with pharmaceutical excipients, mannitol, aspartame, anise & mint flavors, saccharin sodium and potassium bicarbonate to a combined content weight of 900 mg. Potassium bicarbonate is employed as a buffering agent (b) (4) The quality of all excipients is assured either through their compliance with compendia standards or through in-house specification. The manufacturing process consists of a simple (b) (4) The homogeneity of the final (b) (4) and content uniformity were verified by stratified sampling in process validation. The powder formulation is filled and packaged in (b) (4) sealed foil pouch (sachet) (b) (4)

(b) (4) to provide physical and chemical stability of the powder formulation and child resistant packaging. The quality of the drug product is assured through appropriate in-process controls and the final product specification. The final drug product specification include tests and limits for appearance, average weight of content, uniformity of mass, completeness of solution, identification (by TLC and HPLC), assay (HPLC), impurities (HPLC), dissolution, content uniformity and microbial contents. All analytical methods used for drug product testing have been adequately described and validated.

Drug product stability data for three registration batches packaged in the primary packaging configuration intended for marketing were provided for up to 9 months. (b) (4) An 18-month expiration date is recommended for the drug product stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature) based on the evaluation of provided stability data for the registration batches and supporting stability data.

The Office of Compliance has provided an overall acceptable recommendation for the manufacturing sites.

Recommendation: All CMC related issues had been resolved for this application. The application is recommended for **"Approval"** from the CMC perspective. The applicant has agreed to the use of "diclofenac potassium for oral solution" as the established name. A consistent use of this name in the labeling should be ensured during final labeling negotiations. Moreover, the review of the proposed trade name "Cambia" is not complete and a recommendation is pending by DMEPA.

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/s/

Ramesh Sood
10/8/2008 09:46:12 AM
CHEMIST

NDA 22-165

PRO-513
Diclofenac Potassium
Powder for Oral Solution

ProEthic Pharmaceuticals

Division of Neurology Drug Products, HFD 120

Shastri Bhamidipati,
Office of New Drug Quality Assessment,
Division of Pre-Marketing Assessment I

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-165

2. REVIEW #: 1

3. REVIEW DATE: 29-FEB-2008

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-165 Original Submission	29-JUN-2007
NDA 22-165 Amendment(BC)	24-JUL-2007
NDA 22-165 Resubmssion	28-SEP-2007
NDA 22-165 Amendment (BC)	30-OCT-2007
NDA 22-165 Amendment (BC)	18-MAR-2008
NDA 22-165 Amendment (BZ)	22-JUL-2008

7. NAME & ADDRESS OF APPLICANT:

Name: ProEthics Pharmaceuticals, Inc.

Address: 212 South Tryon Street, Suite# 1280
Charlotte, NC 28281

Representative: William R. Maichle, Ph.D.
Sr. Vice President, Product Development
212 South Tryon Street, Suite# 1280
Charlotte, NC 28281

Telephone: (704) 831-6298

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not provided at this time
b) Non-Proprietary Name (USAN): Diclofenac potassium
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.54 , 505(b)(2)

10. PHARMACOL. CATEGORY: Neurology, Migraine

11. DOSAGE FORM: Powder for Oral Solution

12. STRENGTH/POTENCY: 50 mg

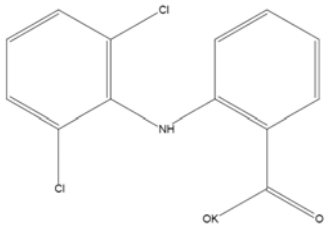
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
   2-(2,6-Dichlorophenyl)amino]benzeneacetate, potassium salt
   Molecular Formula: $C_{14}H_{10}Cl_2KNO_2$
   Molecular Weight: 334.24
   CAS: 15307-81-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4) (b) (4)	Diclofenac Potassium (drug substance)	1	Adequate	29-FEB-2008 16-SEP-2008	Deficiency letter sent to the holder and the amendment submitted in response was reviewed
(b) (4)	III	(b) (4)		4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PRO 513	IND 73073	Diclofenac potassium oral solution

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Acceptable	06-SEPT-2008	S. Adams
Pharm/Tox	Not applicable		
Clinical Pharmacology	Acceptable	27-SEPT-2008	C. Noory
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Trade name review pending.		
EA	Categorical Exclusion granted		
Microbiology	Not applicable as this is solid oral dosage form		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-165

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application for Diclofenac Potassium Powder for Oral Solution can be approved (AP) from CMC perspective. The sponsor adequately responded and satisfactorily addressed all the CMC issues communicated through information request letter on 29-APR-2008. Office of Compliance has provided an overall acceptable recommendation for the manufacturing facilities. The sponsor submitted the trade name, Cambia, for the drug product in their amendment (dated 22-JUL-2008) which is pending review by the Division of Medication Error Prevention and Analysis (DMEPA). The sponsor has revised the established name of the drug product to "Diclofenac Potassium for Oral Solution" and it should be ensured at the time of labeling negotiations that the correct established name is consistently used.

Note: PRO-513 (*in lieu* of the trade name) and Diclofenac Potassium Powder for Oral Solution are the drug product name and description used by the sponsor in the original submission and throughout this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Diclofenac , either in Sodium salt or Potassium salt form, is a non steroidal anti-inflammatory drug with analgesic and antipyretic actions. Both Sodium and Potassium salt forms of Diclofenac formulated as tablets (extended and delayed release), solution for ophthalmic drops and topical gel are currently approved by the Agency for marketing in U.S. The proposed drug product, PRO-513 formulated as powder for oral administration after constituting to a solution in water, was submitted as a 505 (b)(2) NDA and based upon reference to three approved NDAs for Cataflam® (Diclofenac Potassium immediate release tablets, 50 mg ; NDA 20-142), Voltaren® (Diclofenac Sodium enteric coated tablets,25, 50, 75 mg ;NDA 19-241) and Voltaren® XR (Diclofenac Sodium Extended Release tablets, 100 mg; NDA 20-254) . The drug product will be available in single dose units, 'sachets', of 50 mg of Diclofenac Potassium blended with pharmaceutical excipients, mannitol, aspartame, anise & mint flavors, saccharin sodium and potassium bicarbonate to a combined content weight of

900 mg. Potassium bicarbonate is employed [redacted] as buffering agent [redacted] The pharmaceutical development of the powder formulation adequately evaluated in terms of its [redacted] through the use of mannitol with a mean particle size of [redacted] in the formulation. The manufacturing process consists of simple [redacted] Homogeneity of the final [redacted] and content uniformity were verified by stratified sampling in process validation. The powder formulation was filled and packaged in [redacted] sealed foil pouch (sachet) [redacted] to provide physical and chemical stability of the powder formulation and child resistant packaging. Drug product stability data for three registration batches packaged in the primary packaging configuration intended for marketing were provided up to 9 months. Based on analysis of the data and supportive data from additional process validation batches with a different foil for packaging, 18 month expiration date is recommended as the sponsor proposed. It should be noted that Diclofenac Potassium as powder formulation *albeit* with slightly different excipients [redacted] is currently marketed in Switzerland and other countries for the same indication under the trade name, Voltfast by Novartis Pharmaceuticals.

Drug Substance:
Drug substance, Diclofenac potassium was procured from [redacted] and the CMC information was referenced to type II DMF [redacted] through an LoA. At the site of manufacturing the drug product, the incoming material is tested per USP monograph.

B. Description of How the Drug Product is Intended to be Used

PRO-513 is provided as a powder (50 mg of Diclofenac potassium blended with 850 mg of inactive excipients) filled single-use sachets in sets of three units. The contents of each sachet are to be dissolved in 1-2 ounces (30-60 mL) of drinking water prior to administration. The reconstituted oral solution can not be mixed with food. The contents of the sachet should not be mixed with carbonated or alcoholic drinks. The recommended storage conditions are: " Store at 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F-86°F)."

C. Basis for Approvability or Not-Approval Recommendation

This NDA for Diclofenac Potassium Powder for Oral Solution, 50 mg is recommended for approval (AP) from CMC perspective. The Office of Compliance has provided an overall acceptable recommendation for the manufacturing sites. A

shelf-life of 18 months is recommended for expiration dating of the product based on the 9 month long-term storage stability data submitted.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: Martha Heimann, Ph.D.
Project Manager Name/Date: Lana Chen,

C. CC Block

Original NDA 22-165
DNP (HFD-120)/NDA Division File
DNP(HFD-120)/CSO/L. Chen
ONDQA/DPAI/Chemist/S. Bhamidipati
ONDQA/DPAI /PAL/M. Heimann
ONDQA/DPAI RPM/S. Goldie
ONDQA/DPAI /Branch Chief/R. Sood

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/s/

Shastri P. Bhamidipati
10/7/2008 02:07:49 PM
CHEMIST

Ramesh Sood
10/7/2008 03:12:06 PM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-165
Applicant:	ProEthic Pharmaceuticals
Stamp Date:	29-Jun-2007
PDUFA Date:	29-Apr-2008
Trademark:	TBD. [redacted] (b) (4) are proposed.
Established Name:	Diclofenac potassium
Dosage Form:	Powder for Solution
Route of Administration:	Oral
Indication:	Migraine
PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

Diclofenac (as the potassium or sodium salt) is a widely marketed NSAID with analgesic, anti-inflammatory and antipyretic properties. Currently, a number of dosage forms that contain the active moiety are marketed within the U.S. Approved products include Cataflam® (diclofenac potassium) Tablets, Voltaren® (diclofenac sodium) Delayed Release Tablets and Opthalmic Drops, Voltaren® XR (diclofenac sodium) Extended Release Tablets and Solaraze® (diclofenac sodium) Topical Gel. All of the products named above except Solaraze® are marketed by Novartis Pharmaceuticals; Solaraze is marketed by Bioglan Pharmaceuticals. In the current NDA, ProEthic proposes to market an oral, water-soluble, powdered formulation of diclofenac potassium that is intended for treatment of migraine with or without aura in adults. The product, currently designated as PRO-513, will be available as single dose packets containing 50 mg diclofenac potassium and inactive excipients. [redacted] (b) (4)

Drug Substance

The active ingredient, diclofenac potassium, is a well characterized small molecule with molecular formula $C_{14}H_{10}Cl_2KNO_3$ and molecular weight 334.24. Diclofenac potassium is slightly soluble in water under acidic pH; solubility increases as the pH increases to 7.5.

The bulk drug substance is manufactured by [redacted] (b) (4). DMF [redacted] (b) (4) is cross-referenced for CMC information. The DMF does not appear to have been reviewed previously. Acceptance testing performed by the drug product manufacturer

(Mipharm S.p.A.), and the Mipharm acceptance criteria, are described in the NDA. The applicant notes in the submission that a USP monograph for Diclofenac Potassium will become effective in August, 2007. The USP monograph will include (b) (4) limits for impurities than are allowed by the Mipharm acceptance specification (i.e., NMT (b) (4) each or (b) (4) total versus NMT (b) (4) each or (b) (4) total).

Drug Product

The proposed product is a buffered powder for oral solution that will be available in 50 mg, single dose, packets (sachets). The quantitative composition is given in the applicant's Table 3.3.P.1-1 below.

Table 3.2.P.1.-1. Composition Formulation

Ingredient	Weight	Function	Reference Standard
Diclofenac Potassium	50.0* mg	Active	DMF (b) (4)
Glyceryl Behenate	(b) (4)	(b) (4)	NF
Saccharin Sodium			USP
Anise Flavor			In-house
Potassium Bicarbonate			USP
Mint Flavor			In-house
Aspartame			NF
(b) (4) Mannitol			USP**
(b) (4) Mannitol			USP**
Total	900.0 mg		

* The amount in the table is the theoretical amount for the batch. (b) (4) see sections 3.2.P.2.2.2 and 3.2.P.3.2.

** (b) (4) Mannitol in addition to the USP compendial testing, have an additional (b) (4) specification.

The immediate container (sachet) is a sealed, child-resistant, (b) (4) /12 µm (b) (4) /23 µm (b) (4) (b) (4) The sachets are manufactured in sets of three-side-by-side and joined with two small serrated notches (one at the top and bottom) between each sachet to allow for separation.

The contents of a packet are to be mixed with 1 to 2 ounces (30 to 60 mL) of water immediately prior to use. Potassium carbonate is included in the formulation as a buffer (b) (4) potassium carbonate present in the formulation is maintain a (b) (4). Use of other liquids for reconstitution is not recommended due to the pH dependent solubility profile of the active ingredient.

The drug product manufacturing process is straight-forward. Diclofenac potassium is (b) (4) with the remaining ingredients and the resulting powder (b) (4) filled into sachets. In-process testing includes (b) (4), average fill mass, and uniformity of mass.

The proposed regulatory specifications for Diclofenac Potassium Powder for Oral Solution involve straight-forward analytical procedures. Diclofenac content, content uniformity and related substances are determined using two separate reverse phase HPLC methods which were adapted from the European Pharmacopeia (EP) monograph for Diclofenac Potassium. All known impurities are controlled to NMT (b) (4) each and (b) (4) total. The assay method is also

used as a non-specific identification test in conjunction with a normal phase TLC procedure adapted from the EP monograph.

The application contains somewhat limited stability data (3 months long-term and accelerated for two batches) for the drug packaged in the proposed child-resistant commercial packaging. Additional stability data are provided for three earlier process validation batches packaged in a similar (b) (4) sachet (6 months long-term and accelerated) and for the clinical batch (Lot 20051001) packaged in a (b) (4) sachet (18 months long-term/6 months accelerated). The only difference between the commercial packaging and the packaging used for the earlier process validation batches (b) (4) proposed for the commercial packaging provides additional child-resistance. The stability data package was discussed during the pre-NDA meeting. The sponsor was advised that the earlier process validation batches could be considered primary stability batches if the firm could demonstrate that sachets manufactured with the 23 µm Al (b) (4). The sponsor was also advised that the expiration dating period assigned would be consistent with the extent of data submitted for review.

Critical issues for review

Drug Substance

As rapid dissolution is required for reconstitution, drug substance particle size is considered a critical attribute. Particle size may also impact on content uniformity of the powder (b) (4) and finished product. The impact of drug substance particle size on both product attributes should be considered during evaluation of the applicant's proposed specification. Also, the applicant should be encouraged to harmonize the acceptance criteria for related substances with the upcoming USP monograph.

Drug Product

Although this is a simple dosage form, there are two issues that may impact on the manufacturability and quality of the product.

- *Excipient specifications.* As the product is manufactured as a direct powder (b) (4), variation in excipient particle size may affect content uniformity during the (b) (4) or result in segregation during filling of the sachets. (b) (4) mannitol, (b) (4) used in the formulation and particle size criteria are proposed for (b) (4). The (b) (4) mannitol is stated to provide (b) (4) The rationale for inclusion of the (b) (4) is unclear. Whether acceptance criteria for particle size are needed for the remaining excipients should be evaluated during the review.

- *Packaging process.* As a result of previous discussions with the Agency, the composition of the primary packaging was modified to provide for child-resistant packaging. Use of the child-resistant required a number of modifications to allow for uniform fill weight and adequate sealing of the sachets. Equipment and process changes include redesign of

the [redacted] (b) (4) The effect of the changes on product quality should be assessed.

Additional issues

Fileability. Although it is recommended that the application be filed for review; there are deficiencies related to facility information and DMF references that will need to be addressed by the applicant as quickly as possible. The questions in Attachment 1 should be forwarded to the applicant.

Administrative: A claim for categorical exclusion is provided in Module 1. Categorical exclusion is claimed under 21CFR §25.31(b).

Establishment Evaluation: Two sites are identified as drug substance and drug product manufacturer, respectively. The applicant has not provided full information (including registration numbers and site contacts) in the NDA. Once this information is provided, the facilities listed in Attachment 2, and any additional sites identified by the applicant, should be entered into EES

Labeling/Established Name: Labeled potency of the proposed product is stated as content of diclofenac potassium. Diclofenac potassium is recognized as USAN, as is the corresponding sodium salt. All previously approved products containing either the potassium or the sodium salt have also been labeled in terms of the salt content rather than the equivalent free acid. As the potency statement and USAN name are consistent, use of "diclofenac potassium for oral solution" as the established name is appropriate.

Comments for 74-Day Letter

There are no comments for the 74 day letter

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective; however, the applicant should address the questions listed in Attachment 1 prior to the 45-day filing meeting. The drug substance is a well-characterized small molecule and the active moiety was first approved (as the sodium salt) in 1988. The dosage form is a simple powder [redacted] (b) (4) and no novel manufacturing processes are involved. The submission does not appear to require a review by the Manufacturing Sciences Branch. Assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D. _____
Pharmaceutical Assessment Lead Date

Ramesh Sood, Ph.D. _____
Branch Chief Date

ATTACHMENT 1

Filing Questions for Sponsor

Confirm that [redacted] and Mipharm S.p.A are the only manufacturers involved in manufacturing, packaging and testing of Diclofenac Potassium for Oral Solution.

Clarify whether the [redacted] manufacturing facility is located at [redacted] as stated on Form 356h, or at [redacted], as stated on the letter of authorization to DMF [redacted]

Provide site contact information (i.e., contact name, phone number and/e-mail address) and registration numbers (CFN or FEI) for both the [redacted] and Mipharm manufacturing facilities.

Provide an updated letter of authorization to the [redacted] DMF submitted to the Agency on May 17, 2007. The letter of authorization should include the DMF number assigned by the Agency.

ATTACHMENT 2

Manufacturing Sites for Diclofenac Potassium for Oral Solution

Facility Information	Function
(b) (4) Registration No. Site Contact: Tel. No.	Drug substance manufacturer
Mipharm S.p.A Via Quaranta, 12 20141 – Milano (MI) Italy Registration No. Site Contact: Tel. No.	Manufacture, control, primary and secondary packaging and batch release of the drug product

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/s/

Martha Heimann
7/13/2007 10:53:42 AM
CHEMIST

Ramesh Sood
7/13/2007 11:17:55 AM
CHEMIST